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Noise in Biological Membranes and Relevant Ionic Systems

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We review progress in understanding electric noise sources and their physical mechanisms in biological membranes and relevant ionic systems. Specifically, attention is given to noise components whose origin is different from the channel switching between conductance states. Nyquist's formula applications and limitations in model and biological membranes and electrolyte solutions are discussed in view of current experimental data. New experiments on conductance noise in electrolyte solutions, molecule number fluctuations in ion pores, and reversible protonation of the channel-forming molecule residues are presented. Several empirical and model approaches in studies of 1/f noise are critically reviewed. A simple analytical consideration of one-dimensional diffusion noise generation is presented to highlight the potential capacity of diffusion-induced kinetics in noise phenomena description.

ELECTRIC NOISE MEASUREMENTS IN IONIC SYSTEMS were first reported in 1928 by Johnson, who included several second-order conductors in his classical study of equilibrium noise (*1*). Since then a great deal of experimental and theoretical work has been performed. Ever-growing interest in electric noise measurements is motivated by two primary concerns. First, to acquire, process, and transduce information, living organisms use many ionic

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systems. Most popular examples include sensory (such as visual, olfactory, and auditory) signal transduction and nerve impulse propagation along the axonal membrane of neuron cells. Fluctuation phenomena and noise in these biological systems set limits on the sensitivity and reliability of their function. Second, an electric noise is a source of information about the system under study. A classical example is the determination of the value of the electronic charge from the shot noise in vacuum tubes. During the last two decades correlation and spectral analysis of noise in biological and model membranes have provided novel insight into the molecular mechanisms of ionic conduction through these structures.

Use of classification long established in experimental physics enables identification of several sources that contribute to the total noise level in biological membranes In application to membrane ionic transport, such a classification was first introduced by Stevens (*2*). Although these noise sources are not always distinctly different by physical mechanism of noise generation or by spectral features, they can be listed as follows:

1. Johnson noise (equilibrium voltage or current noise)
2. Shot noise (charge transport noise)
3. Conductance noise (impedance modulation noise)
4. $1/f$ noise (flicker noise)

Most review papers on the subject of biological membrane noise have been devoted primarily to conductance noise that arises from channel switching between different conductance states. Several excellent reviews that vary in volume and in mathematical level of presentation of material are available (*3–9*).

The aim of this chapter is to review progress in the field with particular attention to the area that is still developing and is far from complete. Specifically, we discuss noise components that have a different origin from or, at least, are not soundly established as channel switching between conductance states. A number of studies performed with electrolyte solutions and other relevant ionic systems are considered.

Johnson Noise

Ionic systems, such as water solutions of NaCl, $CuSO_4$, K_2CrO_4, and $Ca(NO_3)_2$ and solutions of sulfuric acid in ethyl alcohol, were among the objects of Johnson's experiments (*1*) that led him to conclude that there exists equilibrium electrical noise of a universal nature that manifests thermal motion of charged particles in conductors on a macroscopic level. Independently of a particular conductivity mechanism, the voltage spectral density, $S_V(f)$, of this noise can be calculated from the real part of the system impedance, Re $Z(f)$, by the relation

$$S_V(f) = 4kT \text{ Re } Z(f) \tag{1}$$

where k is the Boltzmann constant and T is the absolute temperature of the system. The spectral density of current noise can be obtained by dividing both sides of this relation by $|Z(f)|^2$, which gives the real part of system admittance on the right-hand side of eq 1.

This relation was proved by Nyquist (*10*) to be a consequence of basic thermodynamics laws and, except for quantum corrections, was never really challenged. Studies performed with glass microelectrodes (*11*) and heterogeneous ionic systems (*12*) showed that for zero ionic gradients and zero applied currents, the measured levels of noise were in agreement with noise levels calculated from the impedance according to eq 1. Hence, a study of electrical noise of a system under equilibrium conditions can be initiated for only two reasons. First, if there is some a priori information that the system is in equilibrium, then measurements of the system impedance or temperature can be performed without external perturbations (quantum effects are not considered here). Second, if impedance and temperature are measured independently by some other techniques, noise measurements can verify that the system under study is in an equilibrium state.

Initial measurements on valinomycin-doped membranes (*13, 14*) showed that lipid bilayers, which provide cells with an effective permeability barrier, are equilibrium objects by this criterion. Within an accuracy of several percent, the experimentally obtained values of the spectral density of voltage noise showed agreement with those calculated from relation 1. Figure 1 illustrates this agreement for three valinomycin concentrations. For the valinomycin–K^+ system chosen for these experiments and for the frequency range used in measurements, the dispersion in membrane impedance was caused only by geometrical capacitance of the bilayer; the characteristic times of the transport process itself were too small to influence impedance in this range.

Similar results that show complete correspondence between noise and impedance (or admittance) in equilibrium conditions were independently reported for lipid bilayers in the presence of hydrophobic ions (*15–17*) and for the valinomycin–Rb^+ transport system (*18*).

Indeed, even nonequilibrium systems do not necessarily show measurable excess noise and, thus, deviate from relation 1. An appropriate example that is relevant to the subject is a capillary channel that contains a stream of electrolyte maintained by an external pressure difference. Measurements on several aqueous polymer solutions with added electrolytes performed at up to 5000 dyn/cm^2 shear stresses and zero external voltage showed that measurable excess noise can be observed only for non-Newtonian solutions exhibiting elasticity (*19, 20*). Similar results were obtained for colloid suspensions

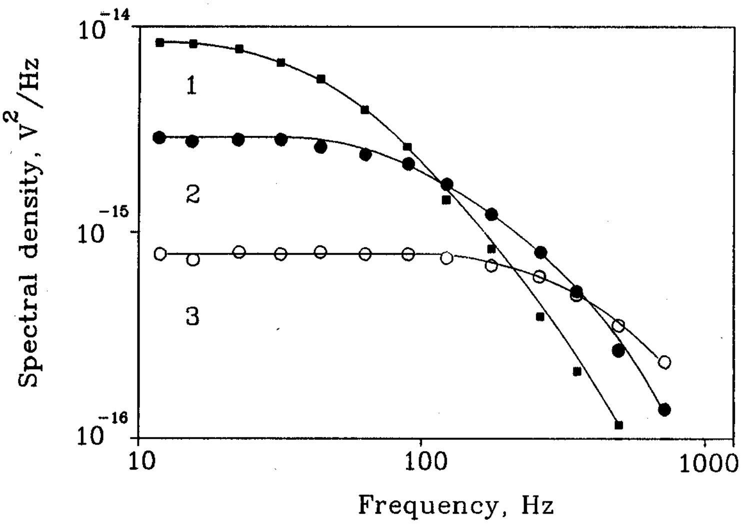

Figure 1. The agreement of the spectral density of voltage fluctuations from valinomycin-modified phospholipid bilayers at equilibrium conditions (13, 14) *with the Nyquist relation 1. An aqueous 0.01-M KCl solution at 33 °C was used in the experiments. Bilayer direct current resistances and valinomycin solution concentrations were 0.52-MΩ and 1.5×10^{-8} M (1), 0.19 MΩ and 5×10^{-8} M (2), and 0.055 MΩ and 1.5×10^{-7} M (3). Solid lines are drawn in accordance with relation 1 for the impedance of a parallel resistance–capacitance (RC) circuit using foregoing resistance values and a value of membrane geometrical capacitance.*

(*21*) and micellar solutions (*22*). In these experiments the differences in noise spectral densities of "unperturbed" electrolyte-filled capillaries and capillaries with maintained flow were below experimental accuracy of several percent.

Transport Noise

The Nyquist relation is no longer valid for nonequilibrium systems. When a nonzero mean electrical current flows through the system, the spectral density of electrical current fluctuations may differ by orders of magnitude from the fluctuations calculated from eq 1.

The first source of nonequilibrium noise, described as early as 1918 (*23*) (in fact 10 years earlier than Johnson noise), was shot noise that stems from the discrete nature of charge transfer. The current spectral density, $S_I(f)$, of this noise is white (independent of frequency f) up to frequencies of the order of the inverse time of elementary charge transfer and is given by

Schottky's formula:

$$S_I(f) = 2q\langle I \rangle \tag{2}$$

where $\langle I \rangle$ is the mean current through the system and q is the charge of flowing particles. This result holds for any system, independent of its complexity, if the transport of charge is unidirectional and charge-transfer events are uncorrelated.

Indeed, for a current pulse $i(t)$ produced as a result of the passage of a single charge-carrying particle, we can write

$$\int_{-\infty}^{\infty} i(t)\, dt = q \tag{3}$$

where q is the charge of the particle. The one-sided spectral density of current noise produced by the uncorrelated sum (i.e., by the Poisson wave) of such pulses is

$$S_I(f) = 2\nu |G(f)|^2 \tag{4}$$

where ν is the average number of pulses per second and

$$G(f) = \int_{-\infty}^{\infty} i(t) \exp(-2\pi jft)\, dt \tag{5}$$

Because of condition 3 the value of $G(f)$ at $f \to 0$ approaches the value of the particle charge. Then we have

$$S_I(f)|_{f\to 0} \to 2\nu q^2 \tag{6}$$

Use of the evident equality $\nu q = \langle I \rangle$ leads to relation 2, which implies that the low-frequency spectral limit of noise produced by unidirectional flow of noninteracting charge carriers is always described by the Schottky formula.

A persistent misconception that multistep charge transfer lowers shot noise exists in the current literature. Several papers devoted to superconductivity problems (*24–26*) make a misleading conclusion about the ability of intermediate stops of vortexes at pinning centers to lower the zero-frequency level of magnetic shot noise. Similar statements about transport in ion channels are found in biophysical literature, as evidenced by a direct quote from reference 27: "If ions pass through a channel in multiple steps, each moving the ion through only a fraction of the width of the membrane, the result will be less transport noise than in the simple shot process." This statement can be true only for very high frequencies that are comparable to the inverse time of ion passage through a channel.

Only correlations between elementary steps of different charge carriers can change the low-frequency shot noise amplitude. The simplest example of such a system, which is shown in Figure 2, is a series arrangement of macroscopic shot noise generators, where each generator for a given mean current $\langle I \rangle$ can be represented by an equivalent circuit that consists of an "ideal" noise generator $2q\langle I \rangle$ in parallel with an "ideal" (noiseless) resistor R. Because the expression $2q\langle I \rangle$ stands for the spectral density and not for the current itself, the noise of the whole arrangement, which is voltage-clamped at terminals A and B, is described by $2q\langle I \rangle / N$. This is clear for the case $N = 2$ and, as a consequence, for any N that is an integral power of 2. Here, the decrease of shot noise amplitude is attributable to "anticorrelations" in transport events that arise from voltage fluctuations in connectors between generators. This simple example illustrates one of the reasons why shot noise is rarely seen in linear macroscopic conductors.

Some useful theoretical approaches have been developed to describe the noise of many special transport mechanisms, such as ion channels, carriers, and electrogenic pumps (*28–33*). Unfortunately, there are few experimental studies of transport noise in biological membranes and lipid bilayers.

A significant contribution was made by Heinemann and Sigworth, who studied noise in open gramicidin channels (*27*, *34*). Remarkably, these authors minimized all other noise sources in the complex reconstitution system so that measurements of transport noise of a single ion channel became possible. In the case of NH_4^+ and Na^+ the measured noise was lower than the noise predicted by the Schottky formula. Heinemann and Sigworth explained this result using a four-state channel model. The model introduces an interaction between ions in such a way that certain anticorrelations arise between moments of successive ion passages through the channel. This anticorrelation results in lowered noise intensity at the frequencies used for spectral measurements.

For K^+, Rb^+, and Cs^+ the level of noise was larger than anticipated for transport noise and could not be described by the model. This noise level

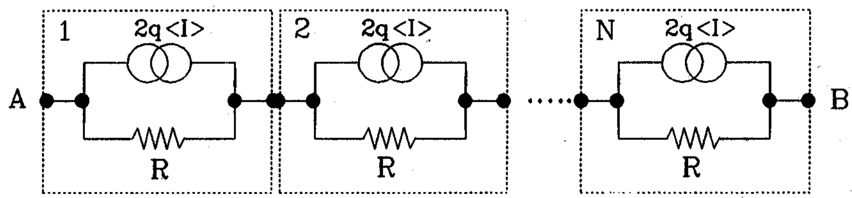

Figure 2. Shot noise damping in a simple model circuit demonstrates why macroscopic linear conductors are usually free from this type of noise. The circuit is a series connection of N *"ideal" current noise generators paralleled by "ideal" resistors. Anticorrelations in elementary transport events arise from the voltage fluctuations in connectors between generators.*

increase was attributed to conformational fluctuations in the channel structure.

Open-channel noise levels in excess of the Schottky formula were also reported in several papers on the same subject (*35–39*). Eisenberg et al. (*39*) obtained a $1/f$ type spectrum for a cation channel of frog lens epithelium. The intensity of the spectrum is orders of magnitude higher than expected for corresponding shot noise. An approximately flat noise spectrum of about 3×10^{-30} A^2/Hz from a potassium channel of lobster sarcoplasmic reticulum was reported by Eisenberg et al. (*40*), who claimed that it was close to the level of the channel Johnson noise.

Nonequilibrium noise generated by carrier-mediated ion transport was studied in lipid bilayers modified by tetranactin (*41*). As expected, deviations of measured spectral density from the values calculated from the Nyquist formula 1 were found. The instantaneous membrane current was described as the superposition of a steady-state current and a fluctuating current, and for the complex admittance in the Nyquist formula only a small-signal part of the total admittance was taken. The justification of this procedure is occasionally discussed in the literature (*see*, for example, Tyagai (*42*) and references cited therein), but is unclear.

A generalization of the Nyquist formula, eq 1, was proposed by Grafov and Levich (*43*) to describe fluctuations in a nonlinear steady state. This approach is based on the fluctuation–dissipation thermodynamics of irreversible nonlinear systems and introduces the so-called dissipative resistance (*42*), which differs from small-signal resistance in a general case. This result indicates that separation of equilibrium and transport noise is not a well-defined procedure.

Conductance Noise

A noise that has a clearly distinct origin from noise discussed in previous sections is the electric noise that originates in modulation of ion transport by fluctuations in system conductance. These temporal fluctuations can be measured, at least in principle, even in systems at equilibrium. Such a measurement was conducted by Voss and Clark in continuous metal films (*44*). The idea of the Voss and Clark experiment was to measure low-frequency fluctuations of the mean-square Johnson noise of the object. In accordance with the Nyquist formula, fluctuations in the system conductance result in fluctuations in the spectral density of its equilibrium noise. Measurement of these fluctuations (that is, measurement of the noise of noise) yields information on conductance fluctuations of the system without the application of any external perturbations. The samples used in these experiments require rather large amplitude conductance fluctuations to be distinguished from Johnson noise fluctuations because of the intrinsic limitation of statistics. Voss and

Clark (*44*) reported successful measurements for a InSb bridge with relative fluctuations as large as $S_G(f)/\langle G\rangle^2 = 10^{-1}$ Hz^{-1} at 10^{-2}-Hz frequency. Here G is conductance of the sample and $S_G(f)$ is spectral density of conductance fluctuations.

In biological ionic systems, conductance noise is induced by membrane structures such as ion channels and fluctuations in electrolyte conductance. Noise that originates from the switching of ion channels between different conductance states has been reviewed extensively (*3–9*). Therefore, we limit ourselves to a discussion of conductance fluctuations in electrolyte solutions (*45*) and new noise sources that have been identified recently for currents through open ion channels (*46, 47*).

An excellent review of the early history of noise studies of different ionic systems, such as single pores in thin dielectric films, microelectrodes, and synthetic membranes, is reference 3. The review by Weissman (*48*) describes several state-of-the-art fluctuation spectroscopy methods that include (1) determination of chemical kinetics from conductivity fluctuations in salt solutions, (2) observation of conductivity noise that arises from enthalpy fluctuations in the electrolyte with high temperature coefficient of resistivity, and (3) detection of large conductivity fluctuations in a binary mixture near its critical point.

Fluctuation phenomena in ionic solutions are a subject of growing interest (*49–51*). However, for several reasons (*48*), experimental approaches to studies of conductance fluctuations in liquid phase samples are not as well established as those in the solid state. Strong electric fields that are used to measure conductance fluctuations (to produce noise in excess of the Johnson noise) cause pronounced electroosmotic and electrophoretic complications. As a result, the measurements of conductance fluctuations are usually made with a significant uncertainty factor (cited as 0.4 in reference 52).

In principle, as far as homogeneous and stationary objects are concerned, two alternative methods can be used to measure a single-time correlator of conductance fluctuations. One method is to instantaneously divide the sample volume (using a hypothetical procedure) into a set of identical elements, for instance, cubes. After the conductance G of each of the cubes is determined, the standard deviation of the conductance from the mean value is found. The other method is based on a sufficiently long (unperturbing) observation of the conductance of a particular element that communicates with an outer ion reservoir. Equilibrium exchange of ions between the element and the rest of the sample will give rise to conductance fluctuations, and the standard deviation is obtained from consecutive readings. For ergodic systems, both methods should provide identical answers with an accuracy dependent on the number of elements processed or on the measurement (observation) time.

A method of large-scale conductance fluctuation measurements in flowing ionic solutions was developed (*21*) recently to measure the space average squared value of these fluctuations with an accuracy of several percent. This method is similar in nature to the procedure of dividing the electrolyte volume into a set of identical elements. The laminar electrolyte flow consecutively changes elements of the volume in a capillary and determines the fluctuation spectrum by its velocity profile. Parameters of the capillary and the hydrostatic pressure difference can be selected to minimize the effect of diffusion and electrokinetic phenomena. This approach eliminates the uncertainties inherent in other experimental setups and substantially increases the absolute accuracy of the conductance fluctuation measurements.

The foregoing method was used to study fluctuations in solutions of strong electrolytes (*45*) and in ionogenic and nonionogenic micellar colloids (*22*). Strong electrolytes were chosen to represent 1:1 electrolytes with nearly equal (NaCl) and significantly different (HCl) mobilities of anions and cations and a 2:1 electrolyte ($CaCl_2$).

The results of these measurements are shown in Figure 3 as the dimensionless value $\langle(\delta G)^2\rangle/\langle G\rangle^2$. The uppermost solid straight line is drawn so that the relative mean square value of fluctuations is normalized to the total number of dissolved electrolyte molecules, N_M; that is,

$$\frac{\langle(\delta G)^2\rangle}{\langle G\rangle^2} = \frac{1}{N_M} \tag{7}$$

The central and bottom straight lines are normalized with respect to a double and triple number of molecules, respectively. Analysis of the experimental dependencies shows that as the electrolyte concentration decreases, the fluctuation level approaches the value anticipated for a system of identical noninteracting particles. This trend is observed both for NaCl and HCl, 1:1 electrolytes that yield two ions per dissolved molecule, and for $CaCl_2$, a 2:1 electrolyte that dissociates into one doubly charged and two singly charged ions.

This "ideal gas behavior" of conductance fluctuations appears to be rather unaccountable. First, electrolyte solutions are systems with pronounced interactions that are attributable to a slow decrease of Coulomb forces between ions; this brings about substantial correlation between mutual positions of ions in space. Second, even in the hypothetical case of weakly interacting charge carriers, the conductance fluctuation level is expected to be equal to the value calculated from the total number of carriers only when the mobilities of different carriers are identical. Indeed, substantial difference in mobilities, say for a 1:1 electrolyte, forces lower mobility carriers to be electrically "invisible" and, thus, the conductance fluctuations must be normalized only to ion species with higher mobility; that is, to the total number of dissolved molecules. Figure 3 shows that this conclusion contradicts the HCl electrolyte experiments in which the mobility of cations is almost five times as large as that of anions. Nevertheless, the level of

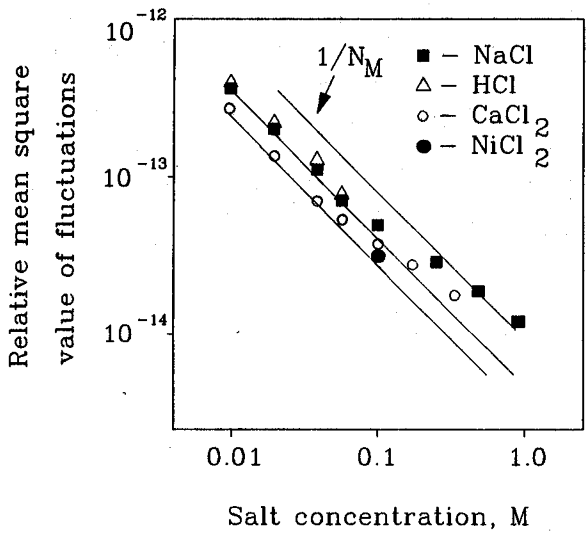

Figure 3. Large-scale conductance fluctuations in aqueous solutions of several strong electrolytes measured by the laminar flow method vs. electrolyte concentration (45). The upper solid line shows the inverse total number of dissolved electrolyte molecules in the sample (that is, in solution volume confined by a fused quartz capillary channel of 13-μm radius and 0.4-mm length). The middle and lower lines correspond to inverse total numbers of ions for 1:1 and 2:1 electrolytes. At small electrolyte concentrations the fluctuation level is within several percent of the inverse number of ions independent of electrolyte type.

conductance fluctuations is close to the value calculated from the normalization that used the total number of ions.

A generalization of the classical result of Lax and Mengert (53) to the case of multicharge ions and combined systems demonstrates that just because of the long-range Coulomb forces between ions, the conductance fluctuation level in dilute simple electrolytes must be normalized to the total number of ions regardless of the electrolyte type and ion mobility difference (45). However, this condition does not hold for complex electrolytes or electrolyte mixtures that contain more than one type of cation or anion. If the mobilities of different types of ions of the same sign are not equal, the fluctuation level would increase so that normalization to the total number of ions in the sample would fail.

A higher fluctuation level compared to the noise of an individual electrolyte was found in the case of NaCl and HCl electrolyte mixtures. The results are presented in Figure 4. Reference solutions of 0.025 M were mixed in different proportions to assure variation of ionic composition while maintaining the total number of ions constant. Mobilities of positive ions, u_{Na} and

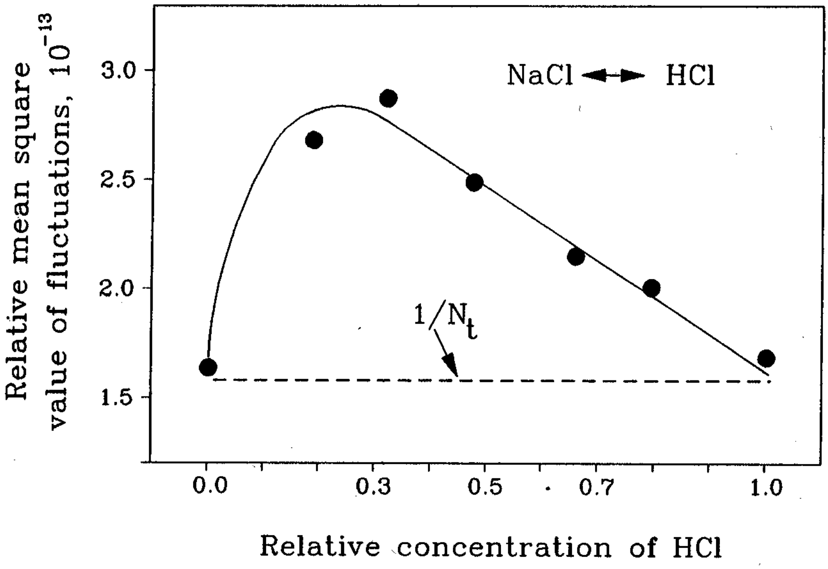

Figure 4. Mixtures of NaCl and HCl electrolytes show higher conductance fluctuations than individual electrolytes (45). The sample composition changes from pure NaCl solution ($K_H = 0.0$) to pure HCl solution ($K_H = 1.0$); the total number of ions is held constant. Experimental points for pure electrolytes are in good agreement with the inverse number of ions in the capillary.

u_H, in dilute solutions of these electrolytes differ approximately by a factor of 7. The solid line is drawn according to theoretical considerations, which give the formula for the deviation of relative conductance fluctuations from the inverse total number of ions in the sample. The ratio θ of fluctuation level in the electrolyte mixture to that in a simple 1:1 electrolyte can be written as (*45*):

$$\theta = 1 + \frac{2K_H(1 - K_H)(u_H - u_{Na})^2}{[u_{Cl} + u_{Na} + K_H(u_H - u_{Na})]^2} \tag{8}$$

where the relative concentration of HCl is defined through proton and sodium concentrations, $K_H = n_H/(n_H + n_{Na})$.

Indeed, much higher levels of conductance fluctuations were reported for electrolytes that contain polystyrene latex suspensions (*21*) or micellar colloids (*22*). Fluctuations were shown to depend on concentration, characteristic size, and the charge of colloid particles. For uncharged nonconductive spherical particles that occupy volume fraction F of the total sample volume

V, excess conductance fluctuations were in agreement with the expression

$$\frac{\langle(\delta G)^2\rangle}{\langle G\rangle^2} = \frac{3}{8}\frac{\pi d^3 F}{V} \tag{9}$$

which directly relates particle diameter d with relative fluctuation level $\langle(\delta G)^2\rangle/\langle G\rangle^2$.

The present results describe an additional source of electrical noise that exists in biological signal transduction media. The contribution of this noise to currents through ion channels can be calculated by considering conductance fluctuations in the region along the convergent ionic paths from the bulk electrolyte medium to the mouth of the channel. Order-of-magnitude estimations show that although electrolyte conductance fluctuations are not important for small single channels where their contribution is significantly below the shot noise level, these fluctuations can be seen in the case of closely packed multichannel arrays and larger transmembrane pores when access resistance (*54*, *55*) is comparable to the resistance of the channel proper.

Two newly identified mechanisms of conductance noise generation in open ion channels were reported recently. Experiments with water-soluble polymers of different molecular weights showed that a "mesoscopic" transmembrane pore formed by alamethicin permits observation of electric noise generated by polymer molecule number fluctuations (*46*). Alamethicin induces aqueous pores of about 10-Å radius that show several conductance levels. These pores are large enough to transport water-soluble polymers with molecular weights up to several thousand daltons. In polymer-free solutions, noise spectra of open-pore currents are frequency-independent in the 40–4000-Hz range and decrease slightly with conductance level number. The magnitude of this noise in 1-M NaCl solutions at 100-mV membrane voltage is comparable but still larger than shot noise anticipated for corresponding currents.

The addition of water-soluble polymers to electrolyte solutions increases open-channel noise. Fluctuations in the number of polymer molecules in the channel produce a supplementary noise component. For polyethylene glycols with 200–10,000-Da molecular weights, this component was white in the frequency range of several kilohertz. Figure 5 presents the spectral density of the open-channel noise averaged over 200–2000 Hz as a function of polymer weight. In contrast to results for polymer-free solutions, the noise grows as the level number increases. Experimental points for polymers smaller than 4000 Da are in agreement with a simple theory of polymer number fluctuations. The theory takes into account the dependence of polymer partition into the channel on polymer weight obtained from the "macroscopic" effect of the polymer addition on channel conductance and permits the estimation of the characteristic time of polymer diffusion through the channel.

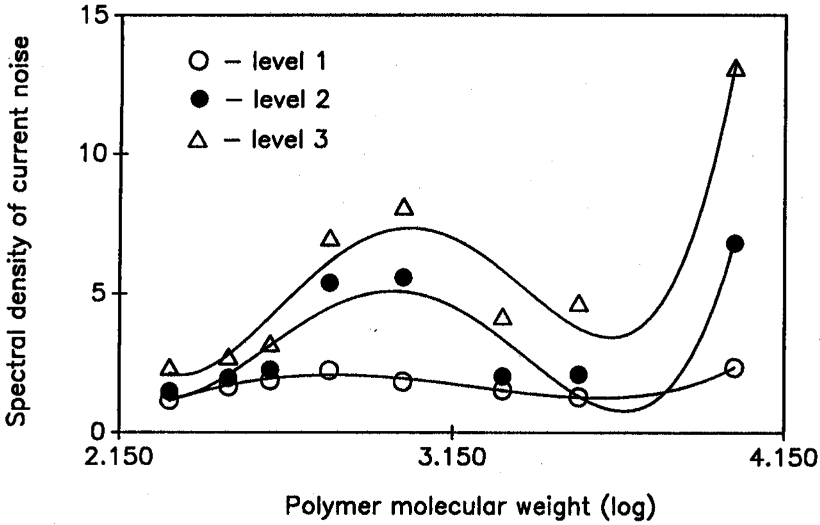

Figure 5. Spectral density of polymer-induced current noise in the open alamethicin channel vs. polymer molecular weight (46). *Data represent noise in different channel-conducting levels at 150 mV in the presence of polyethylene glycols of different sizes added to 1-M NaCl aqueous solutions to obtain 15% weight-to-weight concentration. The vertical scale is given in* 10^{-27} A^2/Hz *units.*

Studies of single channels formed in lipid bilayers by *Staphylococcus aureus* alpha toxin showed that fluctuations in the open-channel current are pH-dependent (*47*). The phenomenon was attributed to conductance noise that arises from reversible ionization of residues in the channel-forming molecule. The pH-dependent spectral density of the noise, shown in Figure 6, is well described by a simple model based on a first-order ionization reaction that permits evaluation of the reaction parameters. This study demonstrates the use of noise analysis to measure the rate constants of rapid and reversible reactions that occur within the lumen of an ion channel.

1/f Noise

Noise with a spectral density that is inversely proportional to frequency over a wide frequency range is a well-known phenomenon found in a great number of quite different objects that include biological membranes and other ionic systems. Extensive reviews of earlier works relevant to membrane biophysics can be found in the literature (*3, 6, 56*).

Multiple reports on the presence of this noise in such a diverse group of systems as carbon resistors, semiconductors, metallic thin films, and aqueous ionic solutions led researchers to believe in the existence of some profound

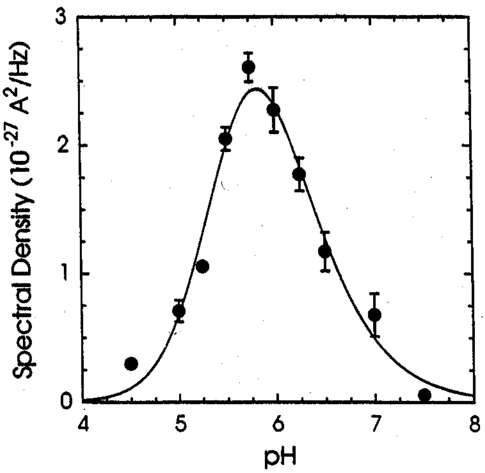

Figure 6. Noise of protonation in the current through an open alpha-toxin channel as a function of pH (47). Spectral density is white at low frequencies and is represented by values averaged over the 200–2000-Hz range. The data were obtained in 1-M NaCl solutions at 150 mV of membrane voltage. The solid line is a two-parameter fit to the first-order ionization reaction that describes a reversible protonation of residues in the channel-forming molecule.

law of nature that applies to all electric conductors and results in $1/f$ noise. This general idea was undoubtedly behind the famous Hooge formula (*57*) that relates the level of $1/f$ noise in the system to the total number of free charge carriers, N_t, through the empirical parameter α:

$$\frac{S_V(f)}{\langle V \rangle^2} = \frac{S_I(f)}{\langle I \rangle^2} = \frac{\alpha}{N_t f} \tag{10}$$

Equation 10 thus states that any dependence of $1/f$ noise on dimensions and the geometry of a particular object can be reduced to the effective value of N_t. Hooge's formula was the subject of criticism in recent literature on noise (*49*, *50*), but, in our opinion, the formula is still most helpful and a popular way to characterize $1/f$ noise of specific systems. As a matter of fact, only 15 years ago the influence of Hooge's empirical relation was so strong that it was used in attempts to solve the inverse problem; that is, to estimate the number of ions in the membrane channel from membrane $1/f$ noise (*58*, *59*).

In early experiments (*60*) the results of electrolyte noise measurements were best described by relation 10 if the dimensionless parameter α was assumed to be proportional to the electrolyte concentration and was taken to be equal to 10 for 1-M aqueous solutions of strong electrolytes.

In later experiments with ionic solutions separated by porous membranes, significant deviations of the magnitude of $1/f$ noise intensity from that predicted by Hooge's formula were found (*61*). For single holes of ~ 5-μm diameter in 12.5-μm-thick Mylar film in 0.1-M KCl aqueous solution, the $1/f$ noise can be described by the much lower value of $\alpha = 10^{-2}$.

Significant deviations from Hooge's formula also were found for ion channels in biological membranes after special difference procedures (*7*) for recording fluctuations from specific channels were introduced. For example, for sodium channels modified by batrachotoxin in myelinated nerve (*62*), the number of mobile ions derived from the formula with the original value of α is nearly 30 times higher than the number of open-membrane channels.

In experiments with amphotericin pores in lipid bilayer membranes (*63*) and with single macroscopic capillaries (*64–66*) filled with carefully purified aqueous solutions of potassium chloride, $1/f$ noise was found to be negligible in comparison with other noise components. The conclusion was that $1/f$ noise in electrolytes is absent with an upper limit on α of about 10^{-3}. De Vos et al. (*67*) suggested that occasionally reported results on measurable $1/f$ noise in electrolytes (*see*, for instance, reference 68) stem from uncontrolled contamination of the samples by inclusions of solid, liquid, or gaseous phases.

The effect of added foreign-phase dispersions on the excess noise in electrolytes was studied (*21, 22*). From relation 15 of Bezrukov et al. (*21*), it follows that the mean-square value of the relative conductance fluctuations that originate from nonconducting contaminants does not depend on the electrolyte concentration. Hence, to present the results of the excess noise measurements in the form of Hooge's formula, with the samples equally contaminated on the average, the parameter α must be taken to be proportional to the electrolyte concentration.

Nevertheless, the phenomenon of membrane $1/f$ noise does exist and cannot be viewed as some artifact that stems from nonoptimal data processing or poor sample preparation. Apart from $1/f$-like spectra reported for thick ($\sim$ 1-mm) synthetic membranes of different types (*see* references 69 and 70 and reviews (*3, 6*) for earlier works), this noise was found in the current and voltage of lipid bilayer membranes modified by several channel-inducing compounds (*71–74*). The first extensive study of $1/f$ spectra was conducted on chemically dimerized gramicidin A by Sauve and Bamberg (*71*). Regular gramicidin A generates a Lorentzian-type power spectrum because of an association–dissociation reaction of transmembrane channel formation. In contrast to regular gramicidin A, the covalently linked dimer exhibits clear $1/f$ noise behavior over several orders of frequency magnitude. The intensity of current noise was proportional to membrane conductance, that is, proportional to the number of channels in the membrane, for three decades of conductance change. Relation 10 well described the current noise intensity if N_i was used to denote the number of channels and $\alpha = 10^{-2}$. Comparison of these results with results obtained for large aqueous pores (*61*) led to the conclusion that $1/f$ noise in this system is related to some general phenomenon of ion transport.

The experimental findings of Sauve and Bamberg were reproduced for several chemically dimerized gramicidin A analogs that had different linking chain lengths (*72–74*). These analogs also produced clear $1/f$ noise. The noise intensity was dependent on the lipid composition of the membrane and proportional to the number of channels over a 100-fold increase in their density in the membrane. The idea of ion transport through the open channel as a source of $1/f$ noise was experimentally tested (*72, 73*). Given the intensity of $1/f$ noise in a multichannel membrane, $S_I(f)$, the mean current through a single open channel, $\langle i \rangle$, and the mean current through a multichannel membrane, $\langle I \rangle$, we can calculate the level of the root-mean-square current fluctuations in the open channel, $\sqrt{\langle(\delta i)^2\rangle}$, if we suppose that these fluctuations should account for noise observed in the multichannel membrane. If τ is the time resolution of single-channel recording and τ_0 is the time of observation, we have

$$\langle \delta i \rangle^2 = \frac{\langle i \rangle}{\langle I \rangle} \int_{(2\pi\tau_0)^{-1}}^{(2\pi\tau)^{-1}} S_I(f)\, df \qquad (11)$$

where the multiplier before the integral is equal to the inverse mean number of simultaneously open channels.

The results of this calculation and comparison to a single-channel recording are presented in Figure 7. The root-mean-square level, which is required to explain $1/f$ noise in membrane current by transport phenomena through the open channel, is much higher than the actual level. The conclusion is that $1/f$ noise in an open channel (if it exists) cannot account for $1/f$ noise in a multichannel membrane.

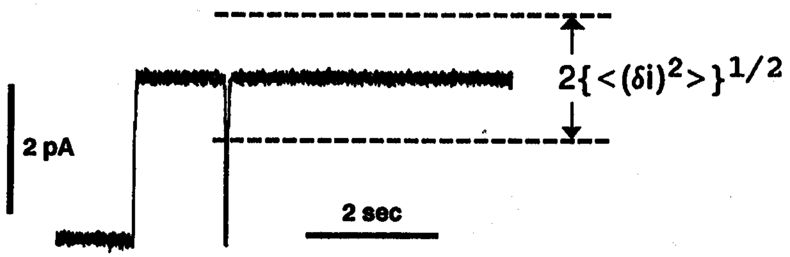

Figure 7. The noise of an open channel formed by chemically dimerized gramicidin A is at least 1 order of magnitude less than the noise required to explain 1/f noise in multichannel membranes (72, 73). Glutaryl-bis-desformylgramicidin was applied at 10^{-16}-M concentration in 1-M aqueous KCl solution bathing a bilayer from glycerol monooleate and cholesterol at 100-mV membrane voltage.

The same system (i.e., a glutaryl-bis-desformylgramicidin channel in a lipid bilayer) was used to study the level of $1/f$ noise in a single channel (*36*, *37*). Only a white component, approximately 1 order of magnitude higher than the level predicted by Schottky's formula, eq 2, was found in the 3–300-Hz frequency range. The origin of this component was not clear and was tentatively attributed to unresolved channel switching to a closed state. This experiment set an upper limit for the possible value of the universal (system-independent) $1/f$ noise in ionic conductors (viz. $\alpha \leq 10^{-5}$). The same value for the limit of α can be inferred from the experiments of Heinemann and Sigworth (*27*, *34*), who reported 1 order of magnitude lower values of white noise component in the gramicidin channel but used some correction procedure for their spectra and 1 order of magnitude higher frequency range. Close values for the upper limit were recently reported for macroscopic capillaries filled with electrolyte solutions (*see* reference 75 and references therein).

A model membrane system that also shows reproducible and clear $1/f$ behavior was described by Bezrukov and Brutyan (*76*). Fluctuations of current through lipid bilayers with one-sided application of three different polyene antibiotics of very close chemical structure (i.e., amphotericin B, nystatin, and mycoheptin) were studied. For one-sided application these antibiotics form channels that are weakly bound to the membrane as compared with the channels of the two-sided action. All three compounds produced pronounced noise component with spectral distribution of $1/f$ type (Figure 8). It was found that the noise intensity scales as the ratio of single channel conductances for amphotericin B, nystatin, and mycoheptin: namely, $h_A:h_N:h_M = 10:5:1$. For mycoheptin the spectrum is described by the function $1/f^{0.86}$ over the whole frequency range used. With two-sided application of these antibiotics, channels are more stable and strongly bound to the bilayer. In this case, significantly lower noise intensities were found; the spectrum for amphotericin B was described by a single Lorentzian spectrum of relatively small amplitude (*63*).

Based on these and earlier findings, a suggestion was made that $1/f$ noise in membranes can arise from diffusion-induced channel transitions between open and closed states (*72–74*, *76*). Channel switching can be generated not only by channel conformational changes, but also as a result of translational or rotational motion of the whole channel that can bring it to a position where it cannot transport ions through the membrane. For weakly bound and easily washable one-sided polyene channels, this channel switching can be the process of equilibrium transitions of antibiotic molecules between solution and membrane. This hypothesis is supported by the strong dependence of $1/f$ noise on membrane lipid composition reported in references 72–74 and by recent work on fractal properties of biological membranes and membrane protein aggregates (*see* references 77 and 78 and references therein).

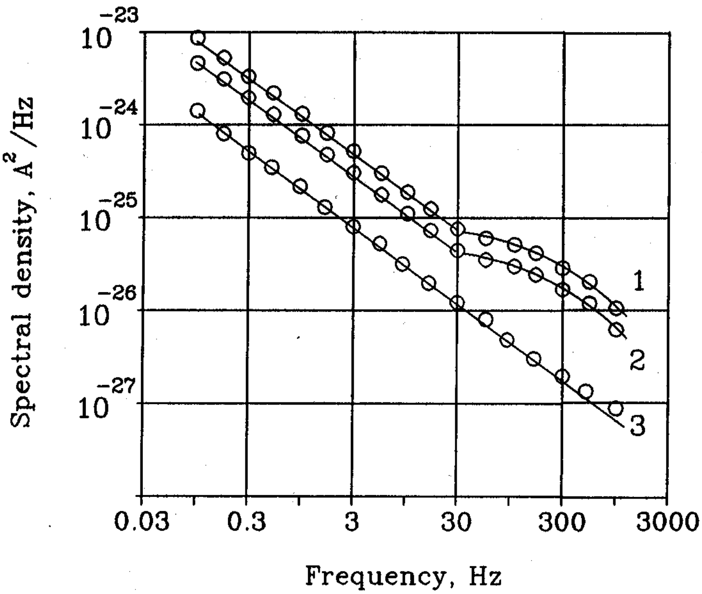

Figure 8. Membrane current noise for one-sided application of three different polyene antibiotics of a very close chemical structure shows 1/f-like spectra with intensities proportional to single-channel conductances for these antibiotics (76). Amphotericin B (1), nystatin (2), and mycoheptin (3) spectra refer to the same membrane conductance of 7.1×10^{-8} S at 10 mV.

The idea of diffusion as a source of $1/f$ noise is rather attractive and indeed was explored by many authors (*79–81*). Diffusion theories that attempted to explain membrane $1/f$ noise by considering fluctuations in the number of charge carriers or diffusion polarization effects were reviewed by Neumcke (*56*).

Recently Gingl and Kiss (*82*) studied the noise of one-dimensional diffusion by computer simulation of the process. Coordinate $x(t)$ of a free particle that undergoes diffusion motion was used as an argument of the function $h(x) = \text{sign}(x)[\text{abs}(x)]^{-k}$ to obtain power spectra of $h(x(t))$ at different values of k. The conclusion drawn from this study was that spectral density $1/f$ corresponds to $k = 0.3$. This result seems to be somewhat inaccurate.

Let us consider this process analytically. We shall calculate the spectrum of noise that arises from free one-dimensional diffusion of a particle, whose coordinate determines the value to be measured. First, let this value be defined as a periodical function of a coordinate that changes abruptly from zero to G_0 at equal intervals 2ι. To visualize the model, imagine a single ion channel that undergoes one-dimensional diffusion through the areas where it can transport ions divided by the areas where it cannot transport ions (Figure

9B). We are interested in the spectrum of noise in conductance $G(x(t))$, which is defined by

$$S_G(f) = 4\int_0^\infty \langle G(x(t))G(x(t+\tau))\rangle \cos(2\pi f\tau)\, d\tau \qquad (12)$$

For a probability $P(x_0, x, \tau)$ to find a particle (channel) in position x at time τ if it was in position x_0 at $\tau = 0$, we can write

$$D\frac{\partial^2 P(x_0, x, \tau)}{\partial x^2} = \frac{\partial P(x_0, x, \tau)}{\partial \tau} \qquad (13)$$

where D is the diffusion coefficient. Because $G(x)$ is an even function with respect to $x = \pm\iota$, we can introduce reflecting walls at these points that do not change the time behavior of $G(x(t))$. This procedure yields conditions $\partial P(x_0, x, \tau)/\partial x = 0$ at $x = \pm\iota$ and permits us to write for the τ-dependent part of the solution of eq 13,

$$P(x_0, x, \tau) = \sum_1^\infty a_n \exp(-\tau/\tau_n)\cos(\pi n x/\iota) \qquad (14)$$

where

$$\tau_n = \iota^2/D(\pi n)^2 \qquad (15)$$

We make use of the condition

$$P(x_0, x, \tau)\big|_{\tau=0} = \delta(x - x_0) \qquad (16)$$

to obtain

$$P(x_0, x, \tau) = (1/\iota)\sum_1^\infty \exp(-\tau/\tau_n)\cos(\pi n x_0/\iota)\cos(\pi n x/\iota) \qquad (17)$$

The autocorrelation function in eq 12 can be written in the form

$$\langle G(x(t))G(x(t+\tau))\rangle = \frac{1}{2\iota}\iint_{-\iota}^{\iota} G(x_0)G(x)P(x_0, x, \tau)\, dx_0\, dx \qquad (18)$$

which gives a straightforward expression for the power spectral density:

$$S_G(f) = \frac{2}{\iota^2}\sum_1^\infty \left[\int_{-\iota}^{\iota} G(x)\cos(\pi n x/\iota)\, dx\right]^2 \frac{\tau_n}{1 + (2\pi f \tau_n)^2} \qquad (19)$$

Spectra calculated for several different functions $G(x)$ are presented in Figure 9. The model of noise at free one-dimensional diffusion can describe

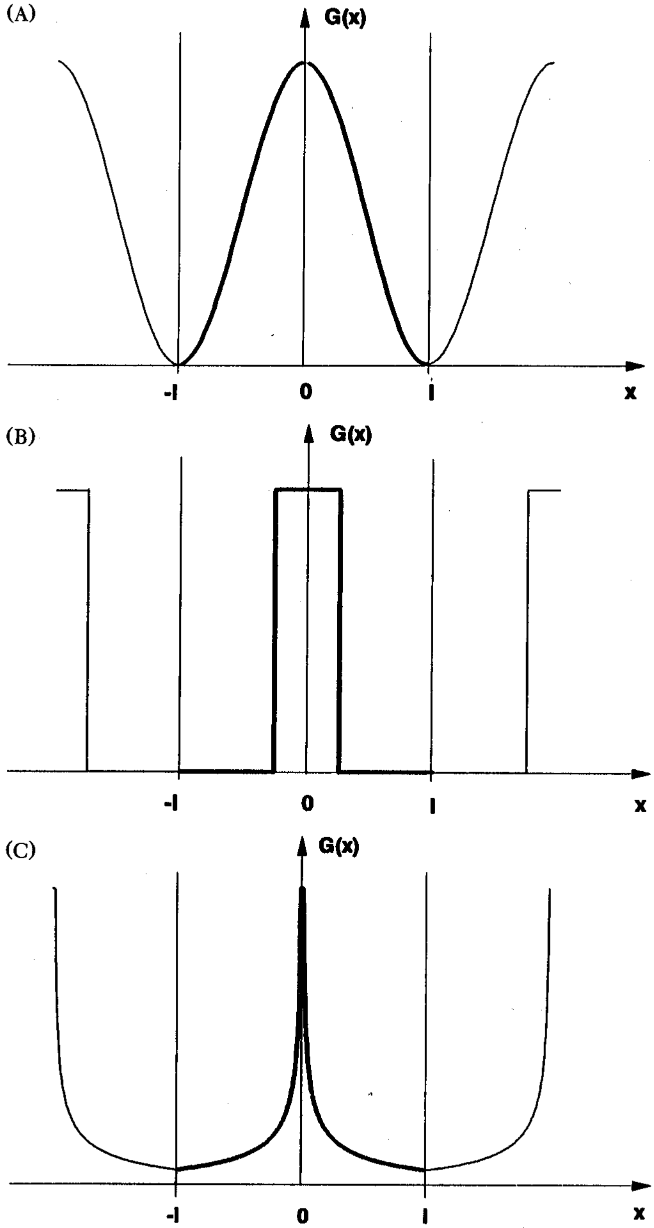

Figure 9. Free one-dimensional diffusion generates fluctuations with practically all types of declining spectra that depend on the choice of the scaling function G(x). *The sine wave scaling function gives a Lorentzian spectrum with the* f^{-2} *high-frequency asymptote (A). The square wave produces a more complex spectrum with an extended* $1/f$*-like region and* $f^{-3/2}$ *high-frequency dependence (B). The* $(abs(x))^{-1/2}$ *scaling function generates noise with a* $1/f$ *spectrum at high frequencies (C). (The actual function used in computations was* $(abs(x) + 10^{-6})^{-1/2}$*.)*

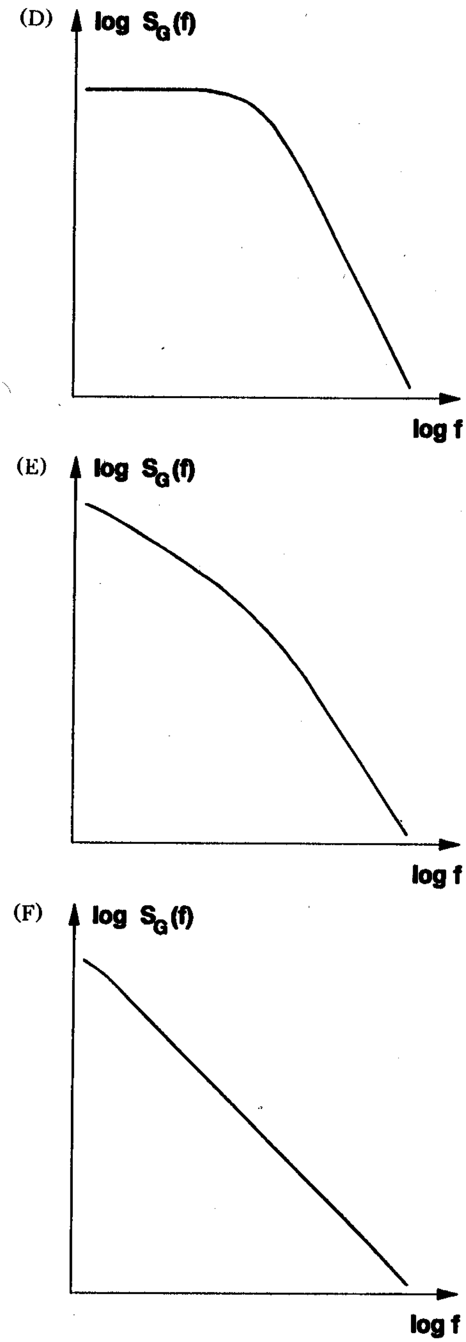

Figure 9. —Continued. *All spectra are plotted in a log–log scale over four decades of frequency change. D, E, and F correspond to A, B, and C, respectively.*

practically any type of noise with declining spectral density. As can easily be seen from eq 19, a sine function for $G(x)$ will produce a Lorentzian spectrum with a f^{-2} high-frequency tail. A square wave will yield a more complex spectrum with $f^{-3/2}$ high-frequency behavior. Two features are worth mentioning. First, even for the simplest model considered, the spectrum has a much longer $1/f$-like region than does a Lorentzian spectrum. Second, the characteristic time, or rather set of characteristic times $\tau_n = \iota^2/D(\pi n)^2$, of the spectrum is proportional to the square of characteristic length ι, which means, for example, that the 100-fold range of fractal scaling found experimentally for many objects (*83*) could lead to 10,000-fold frequency range of $1/f$ noise.

Finally, function $G(x) = (\mathrm{abs}(x))^{-1/2}$ will generate $1/f$ noise at high frequencies. Indeed, try function $G(x) = (\mathrm{abs}(x))^{\mu-1}$. For sufficiently high frequencies (i.e., for large values of n) the integration in eq 19 can be extended to $\pm\infty$, which gives, for the term in square brackets (*84*),

$$2\int_0^{\infty} x^{\mu-1}\cos(\pi n x/\iota)\,dx = \frac{\Gamma(\mu)}{(\pi n/\iota)^{\mu}}\cos\left(\frac{\mu\pi}{2}\right) \qquad (20)$$

if $0 < \mu < 1$. Then, high-frequency asymptotic behavior of the spectral density can be evaluated by integration instead of summation in eq 19 and by making the integral dimensionless with respect to f (*see* also reference 79, page 137). If we omit the details, we have

$$S_G(f) \approx \frac{1}{f^{\mu+1/2}} \qquad (21)$$

so that the $1/f$ spectrum corresponds to $\mu = 1/2$.

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